

# PATENT COOPERATION TREATY

SWABEY OGILVY RENAULT  
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RECEIVED

From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

JUN 29 2000

A.M. P.M.  
PCT 11 12 1 2 3 4 5 6

To:

SWABEY OGILVY RENAULT  
1981 McGill College Avenue  
Suite 1600  
Montréal, Québec H3A 2Y3  
CANADA

WRITTEN OPINION

**DUE ON SEP 21 2000** (PCT Rule 66)

JK

Short Term

Applicant's or agent's file reference <b>13424-1PCT</b> CC		Date of mailing (day/month/year) <b>21.06.2000</b>
International application No. <b>PCT/CA99/00572</b>		REPLY DUE <b>within 3 month(s)</b> from the above date of mailing
International filing date (day/month/year) <b>17/06/1999</b>	Priority date (day/month/year) <b>17/06/1998</b>	
International Patent Classification (IPC) or both national classification and IPC <b>C12N15/11</b>		
Applicant <b>RECHERCHES EXPERTISES ET DEVELOPPEMENT ... et al.</b>		

- This written opinion is the first drawn up by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☒ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☒ Certain document cited
  - VII ☒ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

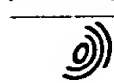
**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 17/10/2000.

Name and mailing address of the international preliminary examining authority:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
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Authorized officer / Examiner

Page, M

Formalities officer (incl. extension of time limits)  
Vullo, C  
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**I. Basis of the opinion**

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*).

**Description, pages:**

1-39 as originally filed

**Claims, No.:**

1-9 as originally filed

**Drawings, sheets:**

1/29-29/29 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**IV. Lack of unity of invention**

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

- ☐ restricted the claims.  
☒ paid additional fees.  
☐ paid additional fees under protest.  
☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons

## WRITTEN OPINION

International application No. PCT/CA99/00572

and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

### V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

#### 1. Statement

Novelty (N)	Claims	1, 2, 4, 6-9: NO 3, 5: YES
Inventive step (IS)	Claims	1, 2, 4-9: NO 3: YES
Industrial applicability (IA)	Claims	1-5: YES 7-9:*

#### 2. Citations and explanations

see separate sheet

### VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

**Re Item IV**

**Lack of unity of invention**

The separate inventions/groups of invention are:

- 1) Oligonucleotides directed against a nucleic acid encoding the CCR3 receptor:  
Claims 1, 5-9 (all partially) and claim 4.
- 2) Oligonucleotides directed against a nucleic acid encoding the common sub-unit  
of the IL-4 and IL-13 receptors: Claims 1, 5-9 (all partially) and claim 2.
- 3) Oligonucleotides directed against a nucleic acid encoding the common sub-unit  
of the IL-3, IL-5 and GM-CSF receptors: Claims 1, 5-9 (all partially) and claim  
3.

In the absence of any common special technical features, these groups of inventions are not considered to be linked as to form a single general inventive concept (Rule 13.1 PCT). The use of antisense oligonucleotides in suppressing the expression of chemokine receptors cannot be regarded as such a feature because this use has been well documented in the prior art.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

The application concerns the provision of antisense oligonucleotides against diverse interleukin receptors for the treatment of various diseases.

- 1) Reference is made to the following documents:  
D1: WO 96 22371 A (BRIGHAM & WOMENS HOSPITAL ;LEUKOSITE INC (US);  
PONATH PAUL D (US);) 25 July 1996 (1996-07-25)  
D2: IKIZAWA K ET AL: 'INHIBITION OF IL-4 RECEPTOR UP-REGULATION ON  
B CELLS ANTISENSE OLIGODEOXYNUCLEOTIDE SUPPRESSES IL-4-  
INDUCED HUMAN IGE PRODUCTION' CLINICAL AND EXPERIMENTAL

- IMMUNOLOGY, vol. 100, no. 3, 1995, pages 383-389, XP000561859 ISSN: 0009-9104
- D3: WO 97 20926 A (SANOFI SA ;CAPUT DANIEL (FR); FERRARA PASCUAL (FR); LAURENT PATRIC) 12 June 1997 (1997-06-12)
- D4: WO 97 28190 A (MEDVET SCIENCE PTY LTD ;LOPEZ ANGEL (AU); BAGLEY CHRISTOPHER (AU);) 7 August 1997 (1997-08-07)
- D5: WO 97 23244 A (SMITHKLINE BEECHAM CORP ;WEN WU DING (US)) 3 July 1997 (1997-07-03)
- D6: WO 97 41154 A (DAUGHERTY BRUCE L ;DEMARTINO JULIE A (US); SICILIANO SALVATORE J () 6 November 1997 (1997-11-06)
- D7: PONATH P D ET AL: 'MOLECULAR CLONING AND CHARACTERIZATION OF A HUMAN EOTAXIN RECEPTOR EXPRESSED SELECTIVELY ON EOSINOPHILS' JOURNAL OF EXPERIMENTAL MEDICINE, vol. 183, June 1996 (1996-06), pages 2437-2448, XP002056313 ISSN: 0022-1007
- D8: WO 97 41225 A (INCYTE PHARMA INC ;COLEMAN ROGER (US); WILDE CRAIG G (US); AU YOUN) 6 November 1997 (1997-11-06)

2) **Novelty - Art.33(1) and (2) PCT:**

**Group 1:** Oligonucleotides directed against a nucleic acid encoding the CCR3 receptor: Claims 1, 5-9 (all partially) and claim 4.

Claims 1, 4 and 6-9 are not new in the light of the prior art. D1 discloses the polynucleotide sequence for CCR3 (D1 SEQ ID NO. 3), antisense oligonucleotides for this gene (page 5 lines 14-18 and claims 46 and 48) and their use in treatment of allergic disease, eosinophilia, inflammation and cancer (pages 58-60).

Claim 5 appears to be new in the light of the prior art, insofar as it applies to group 1 of the application. The SEQ ID NOs. 18-23 are new.

**Group 2:** Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-4 and IL-13 receptors: Claims 1, 5-9 (all partially) and claim 2.

Claims 1, 2, 6 and 7-9 are not new in the light of the prior art. D2 discloses the use of antisense oligonucleotides for the IL-4 receptor and their use in treating allergic reactions (D2 materials and methods page 384, left-hand column §2 and results pages 385-387).

Claim 5 appears to be new in the light of the prior art, insofar as it applies to group 2 of the application. The SEQ ID NOs. 1-7 are new.

**Group 3:** Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1, 5-9 (all partially) and claim 3.

Claims 1, 3 and 5-9 appear to be new in the light of the prior art insofar as they apply to group 3. No reference could be found to antisense oligonucleotides corresponding to the polynucleotide sequence encoding the common beta subunit of the IL-3, IL-5 and GM-CSF receptors.

3) **Inventive Step - Art.33(1) and (3) PCT:**

The following comments on inventive step are confined to subject matter which could be acknowledged as being novel.

**Group 1:** Oligonucleotides directed against a nucleic acid encoding the CCR3 receptor: Claims 1, 5-9 (all partially) and claim 4.

The closest prior art is document D1, which claims antisense oligonucleotides for CCR3 in order to treat allergic disease, eosinophilia, cancer or inflammation (pages 58-60 and claims 46 and 48).

In the light of the prior art, the technical problem can be regarded as the provision of antisense oligonucleotide sequences in order to decrease the expression of CCR3.

The technical problem is solved by the subject matter of claim 5, which provides antisense oligonucleotides for CCR3 (SEQ ID NOs. 18-23). These sequences appear to be obvious in the light of the disclosure of SEQ ID NO. 3 in D1: Although specific sequences have not been previously disclosed, antisense oligonucleotides are suggested in D1 (page 5 lines 14-18). It is a routine matter to then develop antisense oligonucleotides for the known polynucleic acid sequence. It can therefore not be seen where any inventive step might lie.

**Group 2:** Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-4 and IL-13 receptors: Claims 1, 5-9 (all partially) and claim 2.

The closest prior art is document D2, which discloses antisense oligonucleotides for the IL-4 receptor which are effective in limiting IgE production in cells stimulated with IL-4, a model for the allergic response (oligonucleotides 1-3 page 384).

In the light of the prior art, the technical problem can be regarded as the provision of alternative oligonucleotide sequences in order to decrease the expression of the common subunit of the IL-4 and IL-13 receptors.

The technical problem is solved by the subject matter of claim 5, which provides antisense oligonucleotides for the IL-4 receptor (SEQ ID NOs. 1-7). However, oligonucleotide 3 of D2 overlaps with the SEQ ID NOs. 1-3 of the present application. Inventive step cannot be acknowledged merely for alterations of previously disclosed oligonucleotide sequences in the absence of a surprising or unexpected effect. Furthermore, in light of the fact that the polynucleotide sequence for the common subunit of the IL-4 and IL-13 receptors is known, it cannot be seen how SEQ ID NOs. 4-7 can be regarded as being inventive.

**Group 3:** Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1, 5-9 (all partially) and claim 3.

The closest prior art is document D4, which discloses antagonists for the common beta subunit of the IL-3-, IL-5- and GM-CSF-receptor which will block the activation of these receptors (Example 2 on page 17) and are therefore useful in the treatment of allergic reactions with eosiniphilia, such as asthma, as well as leukaemic- and lymphoma-cell proliferation (page 1 lines 17-23, page 2 lines 8-16).

In the light of the prior art, the technical problem can be regarded as the provision of an alternative mechanism for the inhibition of IL-3-, IL-5- and GM-CSF-receptor activation.

The technical problem is solved by the subject matter of claims 1, 3 and 5-9, which provide antisense oligonucleotides for the common subunit of the IL-3-, IL-5- and GM-CSF-receptors (SEQ ID NOs. 8-17). These claims appear to be inventive in the light of the prior art, which does not suggest the present solution in any way.

**4) Industrial Applicability - Art.33(1) and (4) PCT:**

For the assessment of the present claims 7-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**5) Requirements for any Amendments Art. 34(2)(b) PCT:**

Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves,



**WRITTEN OPINION  
SEPARATE SHEET**

International application No. PCT/CA99/00572

and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

**Re Item VI**

**Certain documents cited**

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 99 13886	25.03.99	17.09.98	09.06.98

The above document discloses antisense oligonucleotides for, among other receptors, the IL-3 and IL-5 receptors (SEQ ID NOs. 1102-1115, 1159-1162, 1761-1763 and 1776-1779 and claim 10).

**Re Item VII**

**Certain defects in the international application**

- a) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D8 are not mentioned in the description, nor are these documents identified therein.
- b) Several references to cell amounts in the description appear to be mis-printed, e.g. page 33 line 34 "2.5x10<sup>6</sup> cells/ml". This error should be corrected for the sake of clarity (Art. 5 PCT).

# PATENT COOPERATION TREATY

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RECEIVED

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From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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OCT 19 2000

PCT

A.M.  
7 8 9 10 11 12 1 2 3 4 5 6

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing  
(day/month/year) 13.10.2000

Applicant's or agent's file reference  
13424-1PCT CC

## IMPORTANT NOTIFICATION

International application No.  
PCT/CA99/00572

International filing date (day/month/year)  
17/06/1999

Priority date (day/month/year)  
17/06/1998

Applicant  
RECHERCHES EXPERTISES ET DEVELOPPEMENT ... et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office  
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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>13424-1PCT</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/CA99/00572</b>	International filing date (day/month/year) <b>17/06/1999</b>	Priority date (day/month/year) <b>17/06/1998</b>
International Patent Classification (IPC) or national classification and IPC <b>C12N15/11</b>		
Applicant <b>RECHERCHES EXPERTISES ET DEVELOPPEMENT ... et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 10 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 14 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand <b>14/01/2000</b>	Date of completion of this report <b>13.10.2000</b>
Name and mailing address of the international preliminary examining authority:  <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>Page, M</b>  Telephone No. +49 89 2399 7322



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00572

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

### Description, pages:

1,3-32,34-39	as originally filed		
2,2a-2b,33	as received on	21/09/2000 with letter of	21/09/2000

### Claims, No.:

1-40	as received on	21/09/2000 with letter of	21/09/2000
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### Drawings, sheets:

1/29-29/29	as originally filed
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2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 10-40\*.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/CA99/00572

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 10-40\*.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/CA99/00572

☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 1-40
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-40
	No:	Claims
Industrial applicability (IA)	Yes:	Claims
	No:	Claims 5-7, 24-40 opinion reserved

**2. Citations and explanations**

**see separate sheet**

**VI. Certain documents cited**

**1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

The application concerns the provision of antisense oligonucleotides against diverse interleukin receptors for the treatment of various diseases.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Although the subject matter provided by claims 10-40 is considered to fall outside the scope of the claims as originally filed, in that they seek protection for compositions and methods of treatment using a combination of antisense oligonucleotides directed at different chemokine receptors, opinion is given below with regard to novelty, inventive step and industrial applicability **under the assumption that no relevant prior art exists regarding the combination of appropriate antisense oligonucleotides**. Should such prior art exist, it is probable that the opinion regarding inventive step will be revised at the regional stage.

**Re Item IV**

**Lack of unity of invention**

The separate inventions/groups of invention are:

- 1) Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1-9.
- 2) Combination of oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors and either against the CCR3 receptor or the common subunit of the IL-4 and IL-13 receptors: Claims 10-19 and 24-36.
- 3) Combination of oligonucleotides directed against a nucleic acid encoding the CCR3 receptor and against the common subunit of the IL-4 and IL-13 receptors: Claims 20-23 and 37-40.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA99/00572

In the absence of any common special technical features, these groups of inventions are not considered to be linked as to form a single general inventive concept (Rule 13.1 PCT). The use of antisense oligonucleotides in suppressing the expression of chemokine receptors cannot be regarded as such a feature because this use has been well documented in the prior art (D1, D2).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

- 1) Reference is made to the following documents:
  - D1: WO 96 22371 A (BRIGHAM & WOMENS HOSPITAL ;LEUKOSITE INC (US); PONATH PAUL D (US);) 25 July 1996 (1996-07-25)
  - D2: IKIZAWA K ET AL: 'INHIBITION OF IL-4 RECEPTOR UP-REGULATION ON B CELLS ANTISENSE OLIGODEOXYNUCLEOTIDE SUPPRESSES IL-4-INDUCED HUMAN IGE PRODUCTION' CLINICAL AND EXPERIMENTAL IMMUNOLOGY, vol. 100, no. 3, 1995, pages 383-389, XP000561859 ISSN: 0009-9104
  - D3: WO 97 20926 A (SANOFI SA ;CAPUT DANIEL (FR); FERRARA PASCUAL (FR); LAURENT PATRIC) 12 June 1997 (1997-06-12)
  - D4: WO 97 28190 A (MEDVET SCIENCE PTY LTD ;LOPEZ ANGEL (AU); BAGLEY CHRISTOPHER (AU);) 7 August 1997 (1997-08-07)
  - D5: WO 97 23244 A (SMITHKLINE BEECHAM CORP ;WEN WU DING (US)) 3 July 1997 (1997-07-03)
  - D6: WO 97 41154 A (DAUGHERTY BRUCE L ;DEMARTINO JULIE A (US); SICILIANO SALVATORE J () 6 November 1997 (1997-11-06)
  - D7: PONATH P D ET AL: 'MOLECULAR CLONING AND CHARACTERIZATION OF A HUMAN EOTAXIN RECEPTOR EXPRESSED SELECTIVELY ON EOSINOPHILS' JOURNAL OF EXPERIMENTAL MEDICINE, vol. 183, June 1996 (1996-06), pages 2437-2448, XP002056313 ISSN: 0022-1007
  - D8: WO 97 41225 A (INCYTE PHARMA INC ;COLEMAN ROGER (US); WILDE CRAIG G (US); AU YOUN) 6 November 1997 (1997-11-06)



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA99/00572

**2) Novelty - Art.33(1) and (2) PCT:**

**Group 1:** Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1-9.

Claims 1-9 appear to be new in light of the cited prior art, which nowhere discloses antisense oligonucleotides against the common sub-unit of the IL-3, IL-5 and GM-CSF receptors or their use in treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

**Group 2:** Combination of oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors and either against the CCR3 receptor or the common subunit of the IL-4 and IL-13 receptors: Claims 10-19 and 24-36.

Claims 10-19 and 24-36 appear to be new in light of the cited prior art, which nowhere discloses the combination of antisense oligonucleotides against the common sub-unit of the IL-3, IL-5 and GM-CSF receptors with antisense oligonucleotides directed at other chemokine receptors or their use in treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

**Group 3:** Combination of oligonucleotides directed against a nucleic acid encoding the CCR3 receptor and against the common subunit of the IL-4 and IL-13 receptors: Claims 20-23 and 37-40.

Claims 20-23 and 37-40 appear to be new in light of the cited prior art, which nowhere discloses the combination of antisense oligonucleotides against the common sub-unit of the IL-4 and IL-13 receptors with antisense oligonucleotides directed at the CCR3 receptor or their use in treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

**3) Inventive Step - Art.33(1) and (3) PCT:**

**Group 1:** Oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors: Claims 1-9.

The closest prior art is document D4, which discloses an antagonist to the common subunit of the IL-3, IL-5 and GM-CSF receptors and its use in treating a number of medical conditions (page 7 lines 15-19; page 9 lines 20-23).

In the light of the prior art, the technical problem can be regarded as the provision of an alternative method for inhibiting the activation of the IL-3, IL-5 and GM-CSF receptors.

The technical problem is solved by the subject matter of claims 1-9 which provide antisense oligonucleotides for the common subunit of these receptors and methods of treatment using these compositions.

Because antisense oligonucleotides directed against the common subunit of the IL-3, IL-5 and GM-CSF receptors are not taught in the prior art, the provision of such compounds and their employment must be regarded as demonstrating inventive step.

**Group 2:** Combination of oligonucleotides directed against a nucleic acid encoding the common sub-unit of the IL-3, IL-5 and GM-CSF receptors and either against the CCR3 receptor or the common subunit of the IL-4 and IL-13 receptors: Claims 10-19 and 24-36.

The closest prior art is document D4, which discloses an antagonist to the common subunit of the IL-3, IL-5 and GM-CSF receptors and its use in treating a number of medical conditions (page 7 lines 15-19; page 9 lines 20-23).

In the light of the prior art, the technical problem can be regarded as the provision of an alternative method for inhibiting the allergic response.

The technical problem is solved by the subject matter of claims 10-19 and 24-36,

which provide the combination of antisense oligonucleotides for the common subunit of these receptors, of these antisense oligonucleotides with antisense oligonucleotides directed against either the CCR3 receptor or the common subunit of the IL-4 and IL-13 receptors and methods of treatment using these compositions.

Because antisense oligonucleotides directed against the common subunit of the IL-3, IL-5 and GM-CSF receptors are not taught in the prior art, the combination of these compounds with other antisense oligonucleotides and their employment is regarded as demonstrating inventive step.

**Group 3:** Combination of oligonucleotides directed against a nucleic acid encoding the CCR3 receptor and against the common subunit of the IL-4 and IL-13 receptors: Claims 20-23 and 37-40.

The closest prior art is document D1, which discloses antisense oligonucleotides to the CCR3 receptor and their use for therapeutic purposes (page 5 lines 14-18; page 57 lines 2-3 and 21-29).

In the light of the prior art, the technical problem can be regarded as the provision of an alternative method for inhibiting the allergic response using antisense oligonucleotides.

The technical problem is solved by the subject matter of claims 10-19 and 24-36, which provide the combination of antisense oligonucleotides directed against the CCR3 receptor and the common subunit of the IL-4 and IL-13 receptors and methods of treatment using these compositions.

Because the cited prior art does not contain any motivation to combine antisense oligonucleotides against the CCR3 receptor and the common subunit of the IL-4 and IL-13 receptors, claims 10-19 and 24-36 are regarded as demonstrating inventive step.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA99/00572

**4) Industrial Applicability - Art.33(1) and (4) PCT:**

For the assessment of the present claims 5-7 and 24-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VI**

**Certain documents cited**

**Certain published documents (Rule 70.10)**

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 99 13886	25.03.99	17.09.98	09.06.98

The above document discloses antisense oligonucleotides for, among other receptors, the IL-3 and IL-5 receptors (SEQ ID NOs. 1102-1115, 1159-1162, 1761-1763 and 1776-1779 and claim 10).

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>13424-1pct</b>	<b>FOR FURTHER ACTION</b> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/CA 99/ 00572</b>	International filing date (day/month/year) <b>17/06/1999</b>	(Earliest) Priority Date (day/month/year) <b>17/06/1998</b>
Applicant <b>RECH. EXPERTISES ET DEV. MEDICAUX PARAENZ INC. et</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☒ Unity of invention is lacking (see Box II).

**4. With regard to the title,**

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



None of the figures.

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 99/00572

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although claims 7-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,  
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,5-9 (all partially) and claim 4

Antisense oligonucleotides directed against a nucleic acid encoding the CCR3 receptor, and defined by SEQ IDs 18, 20, 22 and 23. Their use in the preparation of pharmaceutical compositions for the treatment or the prevention of asthma, allergy, hypereosinophilia, inflammation or cancer.

2. Claims: 1,5-9 (all partially) and claim 2

Antisense oligonucleotides directed against a nucleic acid encoding the common sub-units of the IL-4 and IL-13 receptors, and defined by SEQ IDs 1 to 7. Their use in the preparation of pharmaceutical compositions for the treatment or the prevention of asthma, allergy, hypereosinophilia, inflammation or cancer.

3. Claims: 1,5-9 (all partially) and claim 3

Antisense oligonucleotides directed against a nucleic acid encoding the common beta sub-unit of the IL-3, IL-5 and GM-CSF receptors, and defined by SEQ IDs 9 to 16. Their use in the preparation of pharmaceutical compositions for the treatment or the prevention of asthma, allergy, hypereosinophilia, inflammation or cancer.

## INTERNATIONAL SEARCH REPORT

International Application No

T/CA 99/00572

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C12N15/11 A61K31/70 C07H21/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C12N A61K C07H C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 22371 A (BRIGHAM & WOMENS HOSPITAL ; LEUKOSITE INC (US); PONATH PAUL D (US);) 25 July 1996 (1996-07-25) page 17, line 32 -page 18, line 19 page 23, line 10 -page 24, line 22 page 56, line 29 -page 64 claims 46-48 --- -/--	1, 4, 6-9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

8 February 2000

Date of mailing of the international search report

18. 02. 2000

Name and mailing address of the ISA

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Authorized officer

Andres, S



## INTERNATIONAL SEARCH REPORT

International Application No

T/CA 99/00572

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IKIZAWA K ET AL: "INHIBITION OF IL-4 RECEPTOR UP-REGULATION ON B CELLS ANTISENSE OLIGODEOXYNUCLEOTIDE SUPPRESSES IL-4-INDUCED HUMAN IGE PRODUCTION" CLINICAL AND EXPERIMENTAL IMMUNOLOGY, vol. 100, no. 3, 1995, pages 383-389, XP000561859 ISSN: 0009-9104 abstract page 384, left-hand column, line 9 - line 28	1,2,5,7,9
X	WO 97 20926 A (SANOFI SA ;CAPUT DANIEL (FR); FERRARA PASCUAL (FR); LAURENT PATRIC) 12 June 1997 (1997-06-12) page 3, line 7 -page 4, line 15 page 9, line 20 - line 29 examples 7-9 claims 24,25	1,2,6-9
Y	WO 97 28190 A (MEDVET SCIENCE PTY LTD ;LOPEZ ANGEL (AU); BAGLEY CHRISTOPHER (AU);) 7 August 1997 (1997-08-07) page 7, line 15 -page 10, line 4 example 4 claims	1,3,6-9
Y	WO 97 23244 A (SMITHKLINE BEECHAM CORP ;WEN WU DING (US)) 3 July 1997 (1997-07-03) claims 5,6 page 4, line 29 -page 5, line 4	1,3,6-9
X	WO 97 41154 A (DAUGHERTY BRUCE L ;DEMARTINO JULIE A (US); SICILIANO SALVATORE J ( ) 6 November 1997 (1997-11-06) page 10, line 14 -page 13, line 13	1,4,7,9
X	WO 97 22698 A (ICOS CORP) 26 June 1997 (1997-06-26) page 7, line 1 - line 11 page 11, line 24 -page 12, line 18 page 50, SEQ ID 4	1,4,7,9
A	PONATH P D ET AL: "MOLECULAR CLONING AND CHARACTERIZATION OF A HUMAN EOTAXIN RECEPTOR EXPRESSED SELECTIVELY ON EOSINOPHILS" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 183, June 1996 (1996-06), pages 2437-2448, XP002056313 ISSN: 0022-1007	

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/00572

## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 41225 A (INCYTE PHARMA INC ;COLEMAN ROGER (US); WILDE CRAIG G (US); AU YOUN) 6 November 1997 (1997-11-06) page 4, line 4 - line 25 page 22, line 7 -page 24, line 5 page 33, line 10 - line 18 claims 4,16,18,27 ----	1,4-9
A	DEVOS, R. ET AL.: "INTERLEUKIN-5 AND ITS RECEPTOR: A DRUG TARGET FOR EOSINOPHILIA ASSOCIATED WITH CHRONIC ALLERGIC DISEASE" JOURNAL OF LEUKOCYTE BIOLOGY, vol. 57, 1 June 1995 (1995-06-01), pages 813-819, XP002056891 ISSN: 0741-5400 the whole document ----	1,3,6-9
P,X	WO 99 13886 A (NYCE JONATHAN W ;UNIV EAST CAROLINA (US)) 25 March 1999 (1999-03-25) page 7, line 4 -page 9 page 19, line 4 -page 20, line 9 claims 1,2,10,29-42,52-58 -----	1-9

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

/CA 99/00572

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9622371	A	25-07-1996	AU 688206 B	05-03-1998
			AU 5020296 A	07-08-1996
			AU 6994798 A	20-08-1998
			CA 2207086 A	25-07-1996
			EP 0828828 A	18-03-1998
			JP 10512753 T	08-12-1998
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WO 9720926	A	12-06-1997	FR 2742156 A	13-06-1997
			AU 7576096 A	27-06-1997
			BR 9611697 A	17-02-1999
			CA 2238893 A	12-06-1997
			EP 0876482 A	11-11-1998
			JP 11511028 T	28-09-1999
			NO 982550 A	05-08-1998
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WO 9728190	A	07-08-1997	AU 706462 B	17-06-1999
			AU 1536697 A	22-08-1997
			EP 0889905 A	13-01-1999
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WO 9723244	A	03-07-1997	NONE	
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WO 9741154	A	06-11-1997	NONE	
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WO 9722698	A	26-06-1997	AU 1689297 A	14-07-1997
			BR 9607300 A	25-11-1997
			CA 2213331 A	26-06-1997
			CN 1183805 A	03-06-1998
			CZ 9702610 A	17-06-1998
			EP 0811063 A	10-12-1997
			HU 9801127 A	28-08-1998
			JP 11503028 T	23-03-1999
			NO 973800 A	20-10-1997
			PL 321937 A	05-01-1998
			SK 112897 A	08-07-1998
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WO 9741225	A	06-11-1997	AU 2813297 A	19-11-1997
			CA 2252432 A	06-11-1997
			EP 0906424 A	07-04-1999
-----				
WO 9913886	A	25-03-1999	AU 9395198 A	05-04-1999
			WO 9963938 A	16-12-1999
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studies of antisense oligonucleotides as therapeutic agents for cancer and viral diseases.

Few studies have been performed in order to assess whether antisense oligonucleotides could inhibit receptor expression on cell surfaces for inflammatory mediators.

Antisense oligonucleotides can be used to inhibit interleukin (IL)-6 receptor expression and thus the effects of the acute inflammatory mediator interleukin-6 on cells. No studies have been conducted to assess whether antisense oligonucleotides can be employed to inhibit receptors on cells that are involved in asthmatic inflammation or on cancerous cells.

Asthma is a disease that affects 5 to 10% of the population which has doubled in prevalence in the last 25 years. This increase has been noted especially in infants after a viral infection of the airways (bronchiolitis), in children and in occupational induced asthma. The exact cause of asthma is not yet known. However, it is believed that agents such as viruses are involved in the perpetuation of the abnormal inflammation that is found in the airways of patients with asthma and thus the persistence of the disease.

For this reason the current recommendations for first line therapy of asthma is a potent anti-inflammatory medication such as corticosteroids and antileukotrienes. Although this therapy is effective in many patients, some patients are resistant to corticosteroids. This medication is also a potent immunosuppressive with long term side effects and has not been shown to be effective in the prevention of allergy or asthma.

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CCR3 receptor could inhibit the mRNA expression of this receptor on Ghost cells transfected with the CCR3 receptor. These cells were obtained from the NIH and the CCR3 gene was introduced via retroviral infection with MLV BABE-puro vector. It is to be noted in Fig. 21, gel on the right, that the antisense oligonucleotide directed against the CCR3 receptor (RC86A) is effective at inhibiting mRNA expression of the CCR3 receptor when compared to control not incubated with 10 $\mu$ Mol antisense. The gel on the left shows the results obtained for the housekeeping gene G3PDH.

Additional experiments were performed to assess whether antisense oligonucleotides directed against the CCR3 receptor could inhibit the function of this receptor. It is to be noted in Fig. 22 that the antisense oligonucleotide directed against the CCR3 receptor (RC269AS: 5'-CCCTGACATA GTGGATC-3' SEQ ID NO:20 ) and RC86A are effective at inhibiting calcium mobilization (a sign of chemotaxis) in eosinophils. Human eosinophils were purified from blood obtained from patients with asthma by Ficoll Hypaque centrifugation, red blood cell lysis, followed by negative selection with anti-CD16 coated magnetic beads on a MACS cell sorter (to eliminate neutrophils). The eosinophils were then washed and incubated with recombinant human IL-5 (1.6 ng/ml) in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, penicillin, streptomycin, and l-glutamine at 37°C in 5% CO<sub>2</sub> overnight. The cells were washed and then incubated in RPMI 1640 during 4 hours in the presence or absence of 10  $\mu$ M RC269AS or 10 $\mu$ M RC269S 5'-GATCCACTAT GTCAGGG-3' (SEQ ID NO:21) washed and resuspended at 2.5x10<sup>6</sup> cells/ml in RPMI 1640 and incubated with Fura-2M at a concentration of 3 $\mu$ M for 45

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. An antisense oligonucleotide for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said oligonucleotide being directed against a nucleic acid sequence coding for a receptor selected from the group consisting of a CCR3 receptor, a common sub-unit of IL-4 and IL-13 receptors, and a common sub-unit of IL-3, IL-5 and GM-CSF receptors.
2. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the common sub-unit of the IL-4 and IL-13 receptors.
3. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the common beta sub-unit of the IL-3, IL-5 and GM-CSF receptors.
4. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the sub-unit of the CCR3 receptor.
5. The oligonucleotide of claim 1, wherein said oligonucleotide has a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, , SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ

ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:23.

6. A pharmaceutical composition for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said composition comprising at least one antisense oligonucleotide as defined in claim 1, 2, 3, 4 or 5, in association with a pharmaceutically acceptable carrier.

7. Use of an oligonucleotide as defined in claim 1, 2, 3, 4 or 5 for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

8. Use of a pharmaceutical composition as defined in claim 6 for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

9. A method for treating and/or preventing asthma, allergy, general inflammation or cancer, said method comprising the step of administering an effective amount of an oligonucleotide as defined in claim 1, 2, 3, 4 or 5, to a patient in need of such a treatment.

studies of antisense oligonucleotides as therapeutic agents for cancer and viral diseases.

Few studies have been performed in order to assess whether antisense oligonucleotides could inhibit receptor expression on cell surfaces for inflammatory mediators.

Antisense oligonucleotides can be used to inhibit interleukin (IL)-6 receptor expression and thus the effects of the acute inflammatory mediator interleukin-6 on cells. No studies have been conducted to assess whether antisense oligonucleotides can be employed to inhibit receptors on cells that are involved in asthmatic inflammation or on cancerous cells.

International Application published as WO9622371A (Ponath Paul D.) describes the C-C chemokine receptor CKR-3. It is the equivalent of the CCR3 receptor. In the application, there is no preliminary information on whether antisense constructs are effective at inhibiting the CCR-3 receptor. In addition there is no information on the fact that they are effective.

Ikizawa et al. "Inhibition of IL-4 receptor up-regulation on B cells antisense oligodeoxynucleotide suppresses IL-4-induced human IGE production" *Clinical and Experimental Immunology*, Vol. 100, No. 3, pp. 383-389, (1995)", describes antisense oligonucleotides against the IL-4 receptor. There is no mention that this is against the common IL-4 IL-13 receptor. There is no discussion of the common effects with IL-13 or of synergy with IL-13. There is also no discussion of the need to synergize by adding with other oligos.



21-09-2000

- 2a -

International Application published as WO 97 20926, identified the IL-13 receptor alpha and beta sequences. They mention the term antisense oligonucleotides without providing any further information on any sequence or data.

International Application published as WO 9728190 describes the common Beta c receptor for IL-3, IL-5 and GM-CSF. There is no description of the use of antisense oligos for the therapy of allergy, asthma or cancer in any part of the application.

International Application published as WO 97 23244 announces that ODNs are provided which are targeted to the nucleic acid encoding receptor negative regulatory domains. They are targeting genes that encode negative regulatory domains. They are looking at EPO.

International Application WO 97 41154 describes the eosinophil eotaxin receptor that has been designated "CC CKR3". Nowhere in the application is there any sequence or evidence of data for antisense oligonucleotides which can bind to eosinophil eotaxin receptor nucleotides and modulate receptor function or expression".

Ponath PD et al. "Molecular cloning and characterization of a human eotaxin receptor expressed selectively on eosinophils" Journal of Experimental Medicine, Vol. 183, June 1996, pp. 2437-2448, (June 1996), only presents the eotaxin receptor CCR3 sequence.

International Application published as WO9741225A disclose polynucleotides against chemokine receptors for screening. Antisense ODNs are presented

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- 2b -

against the MMLR-CCR or MPHG-CCR chemokine receptors and do not correspond to the receptors of the present invention.

Asthma is a disease that affects 5 to 10% of the population which has doubled in prevalence in the last 25 years. This increase has been noted especially in infants after a viral infection of the airways (bronchiolitis), in children and in occupational induced asthma. The exact cause of asthma is not yet known. However, it is believed that agents such as viruses are involved in the perpetuation of the abnormal inflammation that is found in the airways of patients with asthma and thus the persistence of the disease.

For this reason the current recommendations for first line therapy of asthma is a potent anti-inflammatory medication such as corticosteroids and antileukotrienes. Although this therapy is effective in many patients, some patients are resistant to corticosteroids. This medication is also a potent immunosuppressive with long term side effects and has not been shown to be effective in the prevention of allergy or asthma.

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21-09-2000

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CCR3 receptor could inhibit the mRNA expression of this receptor on Ghost cells transfected with the CCR3 receptor. These cells were obtained from the NIH and the CCR3 gene was introduced via retroviral infection with MLV BABE-puro vector. It is to be noted in Fig. 21, gel on the right, that the antisense oligonucleotide directed against the CCR3 receptor (RC86A) is effective at inhibiting mRNA expression of the CCR3 receptor when compared to control not incubated with 10 $\mu$ Mol antisense. The gel on the left shows the results obtained for the housekeeping gene G3PDH.

Additional experiments were performed to assess whether antisense oligonucleotides directed against the CCR3 receptor could inhibit the function of this receptor. It is to be noted in Fig. 22 that the antisense oligonucleotide directed against the CCR3 receptor (RC269AS: 5'-CCCTGACATA GTGGATC-3' SEQ ID NO:20 ) and RC86A are effective at inhibiting calcium mobilization (a sign of chemotaxis) in eosinophils. Human eosinophils were purified from blood obtained from patients with asthma by Ficoll Hypaque centrifugation, red blood cell lysis, followed by negative selection with anti-CD16 coated magnetic beads on a MACS cell sorter (to eliminate neutrophils). The eosinophils were then washed and incubated with recombinant human IL-5 (1.6 ng/ml) in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, penicillin, streptomycin, and l-glutamine at 37°C in 5% CO<sub>2</sub> overnight. The cells were washed and then incubated in RPMI 1640 during 4 hours in the presence or absence of 10  $\mu$ M RC269AS or 10 $\mu$ M RC269S 5'-GATCCACTAT GTCAGGG-3' (SEQ ID NO:21) washed and resuspended at 2.5x10<sup>6</sup> cells/ml in RPMI 1640 and incubated with Fura-2M at a concentration of 3 $\mu$ M for 45

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## CLAIMS

1. An antisense oligonucleotide for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said oligonucleotide being directed against a nucleic acid sequence coding for a common subunit of the IL-3, IL-5 and GM-CSF receptors.
2. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the common beta sub-unit of the IL-3, IL-5 and GM-CSF receptors.
3. The oligonucleotide of claim 1, wherein said oligonucleotide has a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, , SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:23.
4. A pharmaceutical composition for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said composition comprising at least one antisense oligonucleotide as defined in claim 1, 2 or 3, in association with a pharmaceutically acceptable carrier.
5. Use of an oligonucleotide as defined in claim 1, 2 or 3 for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.
6. Use of a pharmaceutical composition as defined in claim 4 for treating and/or preventing asthma,

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allergy, hypereosinophilia, general inflammation or cancer.

7. A method for treating and/or preventing asthma, allergy, general inflammation or cancer, said method comprising the step of administering an effective amount of an oligonucleotide as defined in claim 1, 2 or 3, to a patient in need of such a treatment.

8. Use of an oligonucleotide as defined in claim 1, 2 or 3 for the manufacture of a medicament for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

9. Use of a pharmaceutical composition as defined in claim 4 for the manufacture of a medicament for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

10. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors.

11. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

12. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

13. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16 and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

14. The pharmaceutical composition according to claim 10, further comprising at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

15. The pharmaceutical composition according to claim 14, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

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16. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

17. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

18. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

19. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16 and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

20. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

21. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

22. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

23. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.



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24. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors.

25. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

26. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

27. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; and at least one oligonucleotide directed

against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

28. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors, at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors, and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

29. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

30. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

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31. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

32. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO: 6, and SEQ ID NO:7; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO: 20, SEQ ID NO:22, and SEQ ID NO:23.

33. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

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34. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

35. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

36. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

37. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and

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IL-13 receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

38. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

39. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

40. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C. 20231  
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 February 2000 (14.02.00)	Applicant's or agent's file reference 13424-1pct
International application No. PCT/CA99/00572	Priority date (day/month/year) 17 June 1998 (17.06.98)
International filing date (day/month/year) 17 June 1999 (17.06.99)	
Applicant RENZI, Paolo	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

14 January 2000 (14.01.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was



was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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**Montreal,  
September 21, 2000**

**International Preliminary Examination Authority  
European Patent Office  
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**Att.: M Page**

**International Patent Application  
No. PCT/CA99/00572 - June 17, 1999  
ANTISENSE OLIGONUCLEOTIDES FOR TREATING  
ATOPIC DISEASES AND NEOPLASTIC CELL  
PROLIFERATION"  
Inventor: Paolo Renzi  
Our ref.: 13424-1"PCT" CC/LM**

**Sir:**

**In response to the Written Opinion mailed June 21, 2000, in connection with  
the above-identified application, please consider the following amendments  
and remarks.**

**DISCLOSURE:**

**Please substitute pages 2, 2a, 2b and 33 submitted herewith for pages 2 and  
33 now on file.**

**CLAIMS:**

**Please substitute the pages containing claims 1 to 40 submitted herewith for  
the pages containing claims 1 to 9 now on file.**

**First of all, Applicant appreciates that the Examiner acknowledged the novelty  
of claims 3 and 5 and the inventive step of claim 3.**

**Novelty**

**In order to overcome the Examiner's rejection of claims 1, 4, and 6 to 9 with  
respect to the novelty of Group 1 of invention, the Examiner will note that**

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claim 1 has been amended to be restricted to the invention of Group 3. Moreover, former claim 4 has also been deleted and the dependency of former claims 6 to 9 has been amended accordingly.

In light of the above, it is respectfully submitted that the Examiner's rejection of claims 1, 4, and 6 to 9, with respect to Group 1 as not being novel in light of the prior art, is respectfully traversed.

Now turning to the Examiner's rejection of claims 1, 2, 6, and 7 to 9 with respect to Group 2 as not being novel in light of the prior art, Applicant wishes to point out that, as mentioned above, claim 1 has been amended to be restricted to Group 3 of invention. Moreover, former claim 2 has also been deleted. The dependency of former claims 6 and 7 to 9 has thus been amended accordingly.

From the above, the Examiner's rejection for lack of novelty of former claims 1, 6 and 7 to 9 with respect to Group 2 is respectfully traversed.

Now turning to Group 3, in the Written Opinion, the Examiner acknowledged that claims 1, 3, and 5 to 9 are novel with respect to invention of Group 3 in view of the prior art.

**Inventive step**

Claims 1, 5 to 9 and 4 have been rejected with respect to Group 1 as being rendered obvious over the prior art cited, and more particularly over document D1.

In this respect, Applicant wishes to point out that the prior claims on CCR3 receptor mentioned the term "antisense" but gave no experiments to back the claims. The Applicant has tried several antisense oligonucleotides directed against the CCR3 receptor that are not effective, such as SEQ ID NO:23 (CCR3A2) and two others directed against the human CCR3 receptor. Two effective antisense oligonucleotides are presented in the present application, i.e. RC86A (SEQ ID NO:18) and RC269AS (SEQ ID NO:20). Although both were effective at inhibiting calcium mobilization in eosinophils, RC269AS was much less effective at inhibiting the CCR3 receptor on GHOST cells transfected with the CCR3 receptor (see Fig. 1). These cells were obtained from the NIH and the CCR3 gene was introduced via retroviral infection with MLV BABE-puro vector. It is to be noted in Fig. 1, that the antisense oligonucleotide directed against the CCR3 receptor (RC86A) is effective at inhibiting mRNA expression of the CCR3 receptor when compared to control not incubated with 10 $\mu$ Mol of antisense. However, the antisense



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oligonucleotide RC269AS at a concentration of 10 $\mu$ Mol was not effective (on the right). The methods for these experiments are described in the patent application. From the above, it can be seen that not all antisense oligonucleotides are effective for treating and/or preventing asthma, allergies, hypereosinophilia, general inflammation or cancer. Only some of them are effective. Therefore, despite SEQ ID NO:3 disclosed in document D1, one skilled in the art could not have arrived at the antisense oligonucleotides as now claim in the present application without involving inventive skills. Accordingly, it is respectfully submitted that former claims 1, 5 to 9 and 4 are inventive over document D1.

With respect to the inventive activity of claims 1, 5 to 9 and claim 2 with respect to Group 2, Applicant notes that all these sequences (SEQ ID NOS:1 to 7 as disclosed in the present application) have the advantage of inhibiting expression of both IL-4 and IL-13. In rejecting the claims for obviousness, the Examiner has cited document D2. However, document D2 did not look at inhibiting both IL-4 and IL-13, but only wanted to inhibit IL-4 alone. Nowhere in his document D1 is there a suggestion or teaching that an attempt was made to inhibit the effects of both mediators. Throughout document D1, the inventor had mentioned only the IL-4 receptor. It is thus the belief of authors of document D2 and within the prior art that inhibition of the IL-4 receptor was sufficient to prevent the production of IgE. Accordingly, Applicant does not believe that document D2 is relevant to the present application as it does not address the inhibition of IL13 mediator. Moreover, the sequences of the antisense oligonucleotides of the present invention, directed towards human common IL-4R and IL-13R receptors chain are different from the antisense disclosed in document D2. Three antisense phosphorothioate oligonucleotides were designed by the authors of document D2 against nucleotides 174-190 (S-oligo 1 : GAG CCC AGA GCA AAG CCA CCC CAT), 199-220 (S-oligo 2 : AGG CAG CTC ACA GGG AAC AG) and 238-258 (S-oligo 3 : ACC TTC ATG TTC CCA GAG CT). S-oligo 1 and S-oligo 2 inhibited the constitutive expression of IL-4 receptor on Daudi cells, while the S-oligo 3 was not effective. Furthermore, only S-oligo 1 was used in all experiments since it displayed the strongest inhibition of the IL-4R expression.

In clear contrast, in the present application, 7 oligo nucleotides have been designed against the common receptors for IL-4 and IL-13. <sup>Three</sup> 3 of these oligonucleotides were on the sub-unit studied by the authors of document D2. Our 3 effective antisense oligonucleotides are directed against nucleotides 241-260 (OD1: 5'AGA CCT TCA TGT TCC CAG AG 3'), 231-250 (OD2: 5' AGG TGG CAA GCT CTG GGA AC 3') and 248-266 (OD3: 5' CCT GCA AGA CCT TCA TGT T 3'). Although OD1, OD2, OD3 and S-oligo 3 are

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overlapping, the authors of document D2 said that S-oligo 3 was not effective (in the same region where the present inventor has designed his effective oligonucleotides). Since the prior art states that the region where the inventor of the present application has designed the antisense is ineffective and since all the antisense oligonucleotides of the present application are in clear contradiction effective, it is respectfully submitted that results presented in the present application are surprising and inventive over document D2. In any event, the Examiner has rejected as mentioned previously, claims 1, 5 to 9 and 4 for lack of inventive activity. However, claim 1 has been restricted to Group 3 of invention, and claim 4 has been deleted. Accordingly, the above argumentation does therefore apply to former claims 5 to 9 now corresponding to new claims 3 to 7.

In view of the above and foregoing, it is respectfully submitted that the claims now on file are clearly inventive over document D2 with respect to Group 2 of invention.

Now turning to Group 3 of invention with respect to inventive activity, the Examiner has acknowledged in the Written Opinion on sheet 5, that claims 1, 3 and 5 to 9 were inventive with respect to Group 3 of invention over the prior art cited.

**Industrial applicability**

Despite the fact that the Examiner has mentioned that there is no unified criteria existing in the PCT contracting states for assessing the industrial applicability of former claims 7 to 9, now corresponding to claims 5 to 7, Applicant preferred nevertheless to maintain these claims in the application as these might be found allowable in some PCT contracting states.

**Re Item VII**

In order to comply with Rule 5.1(a)(II) PCT, page 2 of the disclosure has been amended in order to incorporate a brief discussion of documents D1 to D8 as required by the Examiner.

Furthermore, page 33 of the description has been corrected with respect to the mis-printed cell amounts.

As the Examiner will note, after overcoming all of the Examiner's rejections, new claims have been introduced that also are believed to be novel and inventive over the prior art cited, which relates to synergy between two different antisense targeting two different receptors. These claims are clearly

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supported by the application as originally filed. More particularly, the application as originally filed has already shown that synergy exist between mediators; see Fig. 24 from the patent which shows that priming with IL-5 increases the chemotactic response of eosinophils to eotaxin. It is also reported that the CCR3 receptor is present on eosinophil progenitors (CD34 positive cells) and is involved in eosinophil differentiation. All the ligands that act through the CCR3 receptor synergize with IL-5 to increase eosinophil differentiation.

In the present application, it was also shown that synergy can occur between the antisense oligonucleotides directed against CCR3 and the common Beta-receptor for IL-3, IL-5 and GM-CSF *in vivo* in rats (see Fig. 18B). The dose employed was pre-treatment with 500 µg of ODN intra-peritoneally followed by 200µg of ODN intra-tracheally at the time of antigen challenge. From the above, and more specifically from the results provided in the application as originally filed, there is clear evidence of synergistic effects of a combination of the antisense of the present invention *in vitro* on human cells and *in vivo* in rats (the eosinophilic response after antigen challenge and airway responsiveness to leukotriene D4). There is also evidence in the application that with the antisense of the present invention, it is now possible to convert a non-responder rat into a responder rat. The synergistic effect of combination antisense therapy is not taught or even remotely suggested in the prior art. For example, there is no published information showing the CCR3 receptor, the common Bc receptor or their ligands are involved in TH2 cell differentiation. The simultaneous blockage of genes is contrary to industry practice. Indeed, a non-exhaustive list of programs directed against mediators for the therapy of asthma includes: therapies against one mediator or the use of only one mediator. The combination antisense therapy as suggested in the present application has many advantages that are not even suspected in the prior art, such that it can inhibit the effect of up to 8 mediators.

Therefore, in order to protect these various possible combinations that would allow for synergy of the antisense oligonucleotide of the present invention, new claims 10 to 40 have been added. These claims are originally supported by the description and therefore, no new matter is being hereby introduced. Furthermore, claims 8 and 9 have been introduced. These claims are in the format of Swiss-type use claims which correspond in scope to former claims 7 and 8, now corresponding to claims 5 and 6.

The Examiner will find the specific portion of the application that supports these claims in the Index.

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In view of the above, it is respectfully submitted that all the claims now on file have novelty, inventive step and industrial applicability over the D1 and D8 references identified in the Written Opinion.

It is believed that the Office is now in a position to provide a positive opinion with respect to the claims.

Favourable consideration and a positive International Preliminary Examination Report are requested.

Respectfully submitted,

  
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Enc. Pages 2, 2a, 2b and 33 of the disclosure  
Claims 1 to 40;  
Figure 1 of the drawings;  
Index; and  
EPO 1037.

studies of antisense oligonucleotides as therapeutic agents for cancer and viral diseases.

Few studies have been performed in order to assess whether antisense oligonucleotides could inhibit  
5 receptor expression on cell surfaces for inflammatory mediators.

Antisense oligonucleotides can be used to inhibit interleukin (IL)-6 receptor expression and thus the effects of the acute inflammatory mediator  
10 interleukin-6 on cells. No studies have been conducted to assess whether antisense oligonucleotides can be employed to inhibit receptors on cells that are involved in asthmatic inflammation or on cancerous cells.

15 International Application published as WO9622371A (Ponath Paul D.) describes the C-C chemokine receptor CKR-3. It is the equivalent of the CCR3 receptor. In the application, there is no preliminary information on whether antisense constructs are  
20 effective at inhibiting the CCR-3 receptor. In addition there is no information on the fact that they are effective.

Ikizawa et al. "Inhibition of IL-4 receptor up-regulation on B cells antisense oligodeoxynucleotide  
25 suppresses IL-4-induced human IGE production" *Clinical and Experimental Immunology*, Vol. 100, No. 3, pp. 383-389, (1995)", describes antisense oligonucleotides against the IL-4 receptor. There is no mention that this is against the common IL-4 IL-13 receptor. There  
30 is no discussion of the common effects with IL-13 or of synergy with IL-13. There is also no discussion of the need to synergize by adding with other oligos.

International Application published as WO 97 20926, identified the IL-13 receptor alpha and beta sequences. They mention the term antisense oligonucleotides without providing any further  
5 information on any sequence or data.

International Application published as WO 9728190 describes the common Beta c receptor for IL-3, IL-5 and GM-CSF. There is no description of the use of antisense oligos for the therapy of allergy, asthma or  
10 cancer in any part of the application.

International Application published as WO 97 23244 announces that ODNs are provided which are targeted to the nucleic acid encoding receptor negative regulatory domains. They are targeting genes that  
15 encode negative regulatory domains. They are looking at EPO.

International Application WO 97 41154 describes the eosinophil eotaxin receptor that has been designated "CC CKR3". Nowhere in the application is  
20 there any sequence or evidence of data for antisense oligonucleotides which can bind to eosinophil eotaxin receptor nucleotides and modulate receptor function or expression".

Ponath PD et al. "Molecular cloning and  
25 characterization of a human eotaxin receptor expressed selectively on eosinophils" *Journal of Experimental Medicine*, Vol. 183, June 1996, pp. 2437-2448, (June 1996), only presents the eotaxin receptor CCR3 sequence.

30 International Application published as WO9741225A disclose polynucleotides against chemokine receptors for screening. Antisense ODNs are presented

against the MMLR-CCR or MPHG-CCR chemokine receptors and do not correspond to the receptors of the present invention.

5 Asthma is a disease that affects 5 to 10% of the population which has doubled in prevalence in the last 25 years. This increase has been noted especially in infants after a viral infection of the airways (bronchiolitis), in children and in occupational  
10 induced asthma. The exact cause of asthma is not yet known. However, it is believed that agents such as viruses are involved in the perpetuation of the abnormal inflammation that is found in the airways of patients with asthma and thus the persistence of the disease.

15 For this reason the current recommendations for first line therapy of asthma is a potent anti-inflammatory medication such as corticosteroids and antileukotrienes. Although this therapy is effective in many patients, some patients are resistant to  
20 corticosteroids. This medication is also a potent immunosuppressive with long term side effects and has not been shown to be effective in the prevention of allergy or asthma.

CCR3 receptor could inhibit the mRNA expression of this receptor on Ghost cells transfected with the CCR3 receptor. These cells were obtained from the NIH and the CCR3 gene was introduced via retroviral infection with MLV BABE-puro vector. It is to be noted in Fig. 21, gel on the right, that the antisense oligonucleotide directed against the CCR3 receptor (RC86A) is effective at inhibiting mRNA expression of the CCR3 receptor when compared to control not incubated with 10 $\mu$ Mol antisense. The gel on the left shows the results obtained for the housekeeping gene G3PDH.

Additional experiments were performed to assess whether antisense oligonucleotides directed against the CCR3 receptor could inhibit the function of this receptor. It is to be noted in Fig. 22 that the antisense oligonucleotide directed against the CCR3 receptor (RC269AS: 5'-CCCTGACATA GTGGATC-3' SEQ ID NO:20 ) and RC86A are effective at inhibiting calcium mobilization (a sign of chemotaxis) in eosinophils. Human eosinophils were purified from blood obtained from patients with asthma by Ficoll Hypaque centrifugation, red blood cell lysis, followed by negative selection with anti-CD16 coated magnetic beads on a MACS cell sorter (to eliminate neutrophils). The eosinophils were then washed and incubated with recombinant human IL-5 (1.6 ng/ml) in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, penicillin, streptomycin, and l-glutamine at 37°C in 5% CO<sub>2</sub> overnight. The cells were washed and then incubated in RPMI 1640 during 4 hours in the presence or absence of 10  $\mu$ M RC269AS or 10 $\mu$ M RC269S 5'-GATCCACTAT GTCAGGG-3' (SEQ ID NO:21) washed and resuspended at 2.5x10<sup>6</sup> cells/ml in RPMI 1640 and incubated with Fura-2M at a concentration of 3 $\mu$ M for 45



# CLAIMS

1. An antisense oligonucleotide for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said oligonucleotide being directed against a nucleic acid sequence coding for a common subunit of the IL-3, IL-5 and GM-CSF receptors.
2. The oligonucleotide of claim 1, wherein the nucleic acid sequence coding for the receptor is a nucleic acid coding for the common beta sub-unit of the IL-3, IL-5 and GM-CSF receptors.
- 3 The oligonucleotide of claim 1, wherein said oligonucleotide has a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, , SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:23.
4. A pharmaceutical composition for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, said composition comprising at least one antisense oligonucleotide as defined in claim 1, 2 or 3, in association with a pharmaceutically acceptable carrier.
5. Use of an oligonucleotide as defined in claim 1, 2 or 3 for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.
6. Use of a pharmaceutical composition as defined in claim 4 for treating and/or preventing asthma,

allergy, hypereosinophilia, general inflammation or cancer.

7. A method for treating and/or preventing asthma, allergy, general inflammation or cancer, said method comprising the step of administering an effective amount of an oligonucleotide as defined in claim 1, 2 or 3, to a patient in need of such a treatment.

8. Use of an oligonucleotide as defined in claim 1, 2 or 3 for the manufacture of a medicament for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

9. Use of a pharmaceutical composition as defined in claim 4 for the manufacture of a medicament for treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer.

10. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors.

11. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

12. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

13. The pharmaceutical composition according to claim 10, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16 and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

14. The pharmaceutical composition according to claim 10, further comprising at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

15. The pharmaceutical composition according to claim 14, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

16. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

17. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

18. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

19. The pharmaceutical composition according to claim 16, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16 and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

20. A pharmaceutical composition comprising at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

21. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

22. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

23. The pharmaceutical composition according to claim 20, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

24. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors.

25. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

26. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

27. The method according to claim 24, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; and at least one oligonucleotide directed

against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

28. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors, at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors, and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

29. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

30. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

31. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

32. The method according to claim 28, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO: 6, and SEQ ID NO:7; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO: 20, SEQ ID NO:22, and SEQ ID NO:23.

33. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.



34. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

35. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

36. The method according to claim 33, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-3, IL-5 and GM-CSF receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

37. A method of treating and/or preventing asthma, allergy, hypereosinophilia, general inflammation or cancer, the method comprising administering to a patient at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and

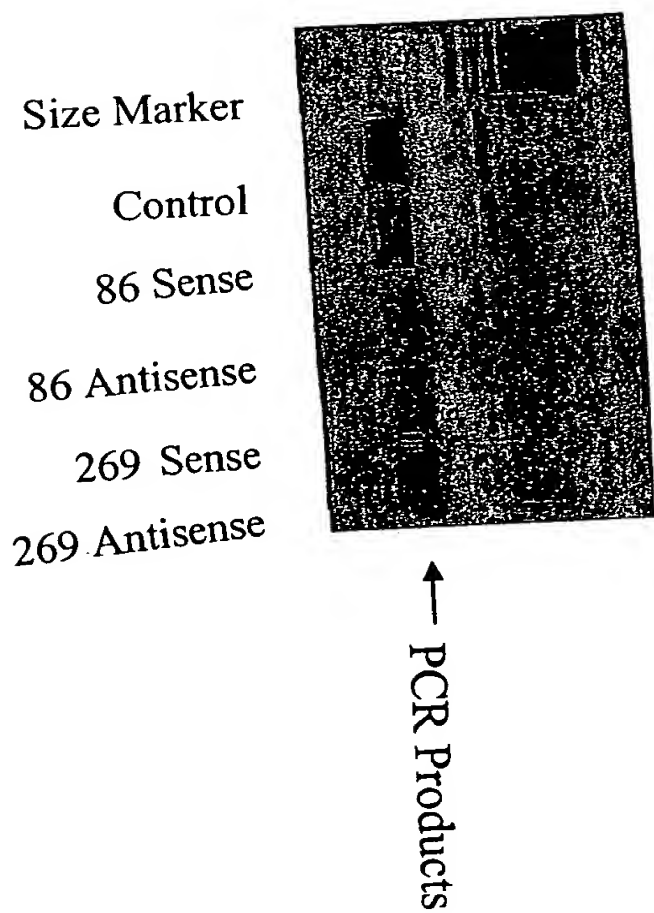
IL-13 receptors and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor.

38. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

39. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

40. The method according to claim 37, wherein at least one oligonucleotide directed against a nucleic acid encoding a common subunit of the IL-4 and IL-13 receptors is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7; and at least one oligonucleotide directed against a nucleic acid encoding a CCR3 receptor is selected from the group consisting of the oligonucleotides listed in the sequence listings as SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:23.

**Figure 1: PCR Test of 2 different CCR3 Antisense  
ODN 's on U937 cells**



INDEX

<u>Original Claim No.</u>	<u>Action</u>	<u>New Claim No.</u>	<u>Supported</u>
1	amended	1	Original claim 1
2	deleted		
3	amended	2	Original claim 3
4	deleted		
5	amended	3	Original claim 5
6	amended	4	Original claim 6
7	amended	5	Original claim 7
8	amended	6	Original claim 8
9	amended	7	Original claim 9
10	New	10	Original claims 7 and 8
11	New	11	Original claims 7 and 8
12	New	12	Original claims 1 and 5
13	New	13	Original claims 1 and 5
14	New	14	Original claim 4
15	New	15	Original claim 5
16	New	16	Original claims 3 and 4
17	New	17	Original claims 3, 4, and 5
18	New	18	Original claims 3, 4 and 5
19	New	19	Original claims 3, 4 and 5
20	New	20	Original claims 2 and 4

21	New	21	Original claims 2, 4 and 5
22	New	22	Original claims 2, 4 and 5
23	New	23	Original claims 2, 4 and 5
24	New	24	Original claims 2, 3 and 9
25	New	25	Original claims 2, 3, 5 and 9
26	New	26	Original claims 2, 3, 5 and 9
27	New	27	Original claims 2, 3, 5 and 9
28	New	28	Original claims 2, 3, and 9
29	New	29	Original claims 2, 3, 5 and 9
30	New	30	Original claims 2, 3, 5 and 9
31	New	31	Original claims 2, 3, 5 and 9
32	New	32	Original claims 5 and 9
33	New	33	Original claims 3 and 4
34	New	34	Original claims 3, 4, 5 and 9
35	New	35	Original claims 3, 4, 5 and 9
36	New	36	Original claims 3, 4, 5 and 9
37	New	37	Original claims 2, 4 and 9

38	New	38	Original claims 2, 4 and 9
39	New	39	Original claims 2, 4 and 9
40	New	40	Original claims 2, 4 and 9

## PCT REQUEST

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0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request Prepared using	PCT-EASY Version 2.84 (updated 01.06.1999)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	Canadian Patent Office (RO/CA)
0-7	Applicant's or agent's file reference	13424-1pct
I	Title of invention	ANTISENSE OLIGONUCLEOTIDES FOR TREATING OR PREVENTING ATOPIC DISEASES AND NEOPLASTIC CELL PROLIFERATION
II	Applicant	applicant only
II-1	This person is:	all designated States except US
II-2	Applicant for	RECHERCHES EXPERTISES ET DÉVELOPPEMENT
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II-9	Facsimile No.	514-896-4677
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III-1-6	State of nationality	CA
III-1-7	State of residence	CA

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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
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IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	CÔTÉ, France; MITCHELL, Robert; HOULE, Guy, J.; MARCOUX, Paul; MURPHY, Kevin, P.; CARRIER, Robert; SOFIA, Michel; ANGLEHART, James; NADEAU, François
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SL SZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AL AM AT AU AZ BA BB BG BR BY CA CH&LI CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW



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V-5	<b>Precautionary Designation Statement</b> In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	<b>Exclusion(s) from precautionary designations</b>	NONE
VI-1	<b>Priority claim of earlier national application</b>	17 June 1998 (17.06.1998)
VI-1-1	Filing date	2,235,420
VI-1-2	Number	CA
VI-1-3	Country	
VI-2	<b>Priority document request</b> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	<b>International Searching Authority Chosen</b>	European Patent Office (EPO) (ISA/EP)
VIII	<b>Check list</b>	number of sheets
VIII-1	Request	4
VIII-2	Description (excluding sequence listing part)	39
VIII-3	Claims	2
VIII-4	Abstract	1
VIII-5	Drawings	31
VIII-6	Sequence listing part of description	6
VIII-7	TOTAL	83
VIII-8	<b>Accompanying items</b>	paper document(s) attached
VIII-8	Fee calculation sheet	✓
VIII-9	Separate signed power of attorney	✓
VIII-15	Nucleotide and/or amino acid sequence listing in computer readable form	separate diskette
VIII-16	PCT-EASY diskette	diskette
VIII-18	Figure of the drawings which should accompany the abstract	1
VIII-19	Language of filing of the international application	English
IX-1	Signature of applicant or agent	<i>Laure Goto</i> CÔTE, France
IX-1-1	Name (LAST, First)	
IX-2	Signature of applicant or agent	<i>Swabe Ogilvy Renault</i> SWABEY OGILVY RENAULT
IX-2-1	Name	

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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

## FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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